

A neuropathic pain syndrome associated with hantavirus infection

Dustin Anderson¹ · Grayson Beecher¹ · Christopher Power¹ · Lindsay Bridgland² · Douglas W. Zochodne¹

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Abstract Hantaviruses are a group of single-stranded RNA viruses of the *Bunyaviridae* family. “New World” hantaviruses cause hantavirus cardiopulmonary syndrome (HCPS) in North America. HCPS carries with it significant mortality and those patients who survive the disease are often left with substantial morbidity. Neurologic complications of hantavirus infections are rare, with only sparse cases of central nervous system involvement having been documented in the literature. To our knowledge, there are no reports of hantavirus infection contributing to peripheral nervous system dysfunction. Here we report a case of possible small fiber neuropathy associated with hantavirus infection, in a patient who survived HCPS. Persistent and treatment-resistant neuropathic pain may be a prominent feature in hantavirus-associated peripheral neuropathy.

Keywords Peripheral neuropathy · Viral infections · Neuropathic pain · Hantavirus

Case report

A 35-year-old previously well male lumber mill worker presented to the Neurology service with severe lower limb neuropathic pain, following discharge from a hospitalization for hantavirus cardiopulmonary syndrome (HCPS). His original presentation was a 5-day history of nausea, vomiting, and general malaise. He had a low-grade fever (38.2 °C), hypotension (90/43 mmHg), tachycardia (155 bpm), and hypoxemia (O₂ saturation 90% on 5 L by nasal prongs). Initial lab results revealed hemoconcentration with a hemoglobin of 202 g/L (normal 135–175 g/L), a leukocytosis of $18.7 \times 10^9/L$ (normal $4.0\text{--}11.0 \times 10^9/L$), and thrombocytopenia of $73 \times 10^9/L$ (normal $140\text{--}450 \times 10^9/L$). He had mild hyponatremia of 130 mmol/L (normal 133–146 mmol/L) and an elevated creatinine of 140 μmol/L (normal 50–115 μmol/L). Chest X-ray demonstrated extensive abnormal reticular markings throughout the lung fields bilaterally (Fig. 1). Worsening hypoxemia prompted intubation and subsequent placement on extracorporeal membrane oxygenation (ECMO), following a trial of standard mechanical ventilation. Hantavirus serology (IgM and IgG) and hantavirus polymerase chain reaction (PCR) were positive in serum. He had a history of exposure to field mice both at work and on a hunting trip in a forested area in central Alberta, Canada, 1 week prior to presentation. Testing for alternative infectious etiologies, including influenza A/B, respiratory syncytial virus, parainfluenza virus, human metapneumovirus, enterovirus, rhinovirus, human coronavirus 229E/NL63/OC43/HKU1, adenovirus, human immunodeficiency virus, mycoplasma pneumoniae, tuberculosis, pneumocystis species, Legionella pneumophila, Francisella tularensis, leptospirosis, Rickettsia rickettsii, Rickettsia typhi, Coxiella burnetii, Yersinia species, and fungal etiologies (by fungal culture from bronchial washings) was negative. Autoimmune work-up including anti-nuclear antibodies, extractable nuclear antigen antibodies, anti-neutrophil cytoplasmic

Dustin Anderson and Grayson Beecher contributed equally to the manuscript.

✉ Douglas W. Zochodne
zochodne@ualberta.ca

¹ Division of Neurology, Department of Medicine, Neuroscience and Mental Health Institute, University of Alberta, 7-132A Clinical Sciences Building, 11350-83 Ave, Edmonton, Alberta T6G 2G3, Canada

² Division of General Internal Medicine, Department of Medicine, University of Alberta, Edmonton, Alberta T6G 2G3, Canada

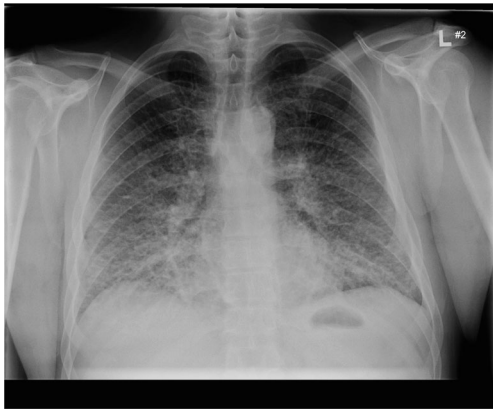


Fig. 1 Postero-anterior radiograph on initial presentation to hospital demonstrating increased reticular markings bilaterally

antibodies, and anti-glomerular basement membrane antibodies was unremarkable. Treatment was supportive, with the patient being decannulated and extubated on days 5 and 8 of admission, respectively. The patient was discharged home following 7 additional days of convalescence.

One month later, he presented to the Neurology service with severe, intractable limb pain that developed 1 week following discharge. He reported burning pain along the plantar aspect of his feet extending to the mid-calves posteriorly. Neurological abnormalities were confined to the sensory system, with severe allodynia to light touch and hyperalgesia to pinprick in a stocking distribution up to the mid-calf bilaterally. His gait was antalgic. There was no limb edema, trophic change, color change, or abnormal sweating. Investigations including complete blood count, electrolytes, calcium, magnesium, creatine kinase, thyroid-stimulating hormone, vitamin B12, hemoglobin A1c, fasting glucose, creatinine, urea, and serum protein electrophoresis were normal. He was discharged on gabapentin and naproxen. At follow-up 4 months later, his limb pain was only marginally improved and he was unable to return to work. He had persistent severe allodynia to light touch over the distal forefoot and plantar great toes bilaterally, with an antalgic gait. Electrophysiological studies including sensory nerve conduction were normal. By 1 year following initial admission, he continued to experience striking allodynic pain, but its intensity had declined.

Discussion

Hantaviruses are a genus of single-stranded RNA viruses that belong to the *Bunyaviridae* family (Kruger et al. 2015). In North America, “New World” hantaviruses cause HCPS (Kruger et al. 2015). This is in contrast to the hantavirus serotype Puumala, prevalent in central and eastern Europe and responsible for the clinical phenotype of hemorrhagic fever with renal syndrome (HFRS) (Alexeyev and Morozov 1995). To date, there have been over 600 cases of HCPS documented in the USA and more than 2000 cases throughout North and South America

(Hartline et al. 2013). Transmission of the virus occurs through the inhalation of aerosolized rodent saliva, urine, or feces (Hartline et al. 2013; Kruger et al. 2015). Patients present with non-specific complaints, including fever, myalgias, headaches, and severe abdominal pain (Hartline et al. 2013; Kruger et al. 2015). Symptoms progress to non-productive cough, tachypnea, hypoxia, and eventual cardiopulmonary collapse (Hartline et al. 2013; Kruger et al. 2015). Treatment is supportive, emphasizing oxygenation and hemodynamic support (Hartline et al. 2013; Kruger et al. 2015). The case fatality rate is approximately 40% in the USA (Hartline et al. 2013). Following the acute phase of HCPS, patients may experience weakness, fatigue, and breathing difficulties for months to years (Jonsson et al. 2008) but there are no reports of neuropathic pain to our knowledge.

Neurologic complications from “New World” hantaviruses are rare, with only sporadic published reports (Huisa et al. 2009). Here we present a case of possible hantavirus-associated neuropathy, in a patient who developed HCPS. Extensive infectious, autoimmune, and metabolic work-up for alternative etiologies was unremarkable. We are not aware of other reports of delayed onset small fiber neuropathy associated with ECMO use. An additional diagnostic consideration in this case would include critical illness polyneuropathy (CIP), as original descriptions of CIP survivors included those with intractable neuropathic pain (Koshy and Zochodnev 2013). Although the patient presented here was critically ill, he did not develop flaccid weakness or sensory loss in the context of his acute illness and his course in hospital was relatively short compared to those patients who develop CIP in the intensive-care unit setting. The dependence on mechanical ventilation due to respiratory musculature weakness that is common to many patients with CIP was not observed in this case. The delayed onset of neuropathic symptoms at 2 weeks following full recovery from critical illness and the lack of electrophysiological changes, including denervation or axon loss, would be further atypical for CIP.

We are not aware of other reports of HCPS associated with peripheral neuropathy. Like selected viruses, including human immunodeficiency virus (HIV), human T-lymphotropic virus-1 (HTLV-1), Epstein-Barr virus (EBV), and varicella-zoster virus (VZV), hantavirus may target sensory neurons either through inflammation at the dorsal root ganglia or through direct axon toxicity. Given the absence of overt sensory loss, it seems unlikely that the major feature was axonal damage, but rather altered sensory neuron membrane properties facilitating neuropathic pain. Whether the sensory neuropathy seen here was caused by direct hantavirus infection or an immune-mediated, post-infectious complication is unknown.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

- Alexeyev OA, Morozov VG (1995) Neurological manifestations of hemorrhagic fever with renal syndrome caused by Puumala virus: review of 811 cases. *Clin Infect Dis* 20(2): 255–258
- Hartline J, Mierek C, Knutson T, Kang C (2013) Hantavirus infection in North America: a clinical review. *Am J Emerg Med* 31:978–982
- Huisa BN, Chapin JE, Adair JC (2009) Central nervous system complications following hanta virus cardiopulmonary syndrome. *J Neuro-Oncol* 15:202–205
- Jonsson CB, Hooper J, Mertz G (2008) Treatment of hantavirus pulmonary syndrome. *Antivir Res* 78:162–169
- Koshy K, Zochodne DW (2013) Neuromuscular complications of critical illness. *Handb Clin Neurol* 115:759–780
- Kruger DH, Figueiredo LT, Song JW, Klempa B (2015) Hantaviruses—globally emerging pathogens. *J Clin Virol* 64:128–136